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Keywords
LORETA · Kurtosis · Epilepsy · Electroencephalography · Theta rhythm

Abstract
Objectives: eLORETA (exact low-resolution brain electromagnetic tomography) is a technique created by Pascual-Marqui et al. [Int J Psychophysiol. 1994 Oct;18(1):49–65] for the 3-dimensional representation of current source density in the brain by electroencephalography (EEG) data. Kurtosis analysis allows for the identification of spiky activity in the brain. In this study, we focused on the evaluation of the reliability of eLORETA kurtosis analysis. For this purpose, the results of eLORETA kurtosis source localization of paroxysmal activity in EEG were compared with those of eLORETA current source density (CSD) analysis of EEG data in 3 epilepsy patients with partial seizures. ***Methods:*** EEG was measured using a digital EEG system with 19 channels. We set the bandpass filter at traditional frequency band settings (1–4, 4–8, 8–15, 15–30, and 30–60 Hz) and 5–10 and 20–70 Hz and performed eLORETA kurtosis to compare the source localization of paroxysmal activity with that of visual interpretation of EEG data and CSD analysis of eLORETA in focal epilepsy patients. ***Results:*** The eLORETA kurtosis analysis of EEG data preprocessed by bandpass filtering from 20 to 70 Hz and traditional frequency band settings did not show any discrete paroxysmal source activity compatible with the results of CSD analysis of eLORETA. In all 3 cases, eLORETA kurtosis analysis filtered at 5–10 Hz showed paroxysmal activities in the theta band, which were all consistent with the visual inspection results and the CSD analysis results. ***Discussion:*** Our findings suggested that eLORETA kurtosis analysis of EEG data might be useful for the identification of spiky paroxysmal activity sources in epilepsy patients. Since EEG is widely used in the clinical practice of epilepsy, eLORETA kurtosis analysis is a promising method that can be applied to epileptic activity mapping.
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Introduction

Epilepsy is one of the most common diseases in the neurological field characterized by epileptic seizures which are caused by excessive and abnormal electrical discharges of the brain. The prevalence rate in the general population is about 0.7–1.0%, and the number of people having epilepsy is about 50 million people in the world [1].

Electroencephalography (EEG) is noninvasive, inexpensive, and widely used in the clinical examination for epilepsy. Unlike for electrocardiography, an automatic analysis function has not yet been implemented for EEG in the clinical setting because of its larger number of channels, more frequent artifacts, and more complicated findings and reports. Identification of the spike localization, including the seizure onset zone, is very important for the diagnosis, classification, and management of epilepsy, especially for presurgical evaluation. However, it is quite time consuming to analyze long-term multichannel EEG signals manually under visual inspection even by certified electroencephalographers. Therefore, computer-based EEG analysis methods to detect epileptic discharges automatically has become an emerging and expanding field of research [2–4].

Quantitative EEG provides computerized imaging and statistical procedures to detect the abnormal patterns of neurological and psychiatric disorders [5, 6]. eLORETA (exact low-resolution brain electromagnetic tomography) is an EEG analysis method developed by Pascual-Marqui [7] for visualizing the distribution of electrical activity sources in the brain. It allows to depict the source localization of electric brain activity from scalp EEG data [8–10]. The current source density (CSD) analysis of eLORETA provides images of CSD with exact localization, albeit with low spatial resolution. We can illustrate the spread of neural activity at about 7-mm spatial resolution. Many previous studies have already demonstrated the feasibility and reliability of the eLORETA method [11–13].

Kurtosis is a statistical method of the "peakedness" or "spikyness" of the probability distribution of a real-valued random variable and a powerful tool in outlier detection, particularly when the number of outliers is unknown [14]. If the kurtosis is larger than the normal distribution, it can be said that it is a distribution with a sharp peak and a long thick tail. If the kurtosis is small compared to the normal distribution, it can be stated that it is a distribution with a more roundish peak and a shorter thin tail. This measure has been used in the source analysis of the magnetoencephalographic (MEG) signal in patients with epilepsy [15]. Previous studies of MEG data have also reported that the synthetic aperture magnetometry (SAM) kurtosis algorithm (SAM[g2]) provides automated detection of spike sources using an excess kurtosis value [15–23]. In some of these previous studies, we performed SAM(g2) analysis of MEG data of epilepsy patients between 20 and 70 Hz to eliminate the background activity and contrast the interictal spike activity. Due to the recent implementation of the kurtosis function in eLORETA, EEG kurtosis analysis may make the detection of spiky activity in the brain possible [24].

In clinical practice of visual EEG inspection, we often observe some focal theta activity in the vicinity of the epileptogenic areas in epilepsy patients. Llinás et al. [25] speculated that pathological theta oscillations often increase in thalamocortical networks. It has also been reported that in animal models of epilepsy increased theta activity showed the seizure-gating effect [26, 27]. Clemens et al. [28] also reported that increased theta activity in some brain areas can be detected as an endophenotype for idiopathic generalized epilepsy. In this study, we emphasize the importance of the pathophysiology of theta rhythms in epilepsy patients.

To localize the sources of scalp-recorded spontaneous theta activity in patients with partial epilepsy, Clemens et al. [28] analyzed interictal EEG data using LORETA in the very narrow band of 1 Hz width. They found that EEG activity in the theta band is increased in anatomically meaningful patterns in partial epilepsy patients and differs from the anatomical distribution of theta rhythm in healthy persons. Particularly, their very narrow band analysis led to astonishing findings according to which activity increased as a function of frequency from 4 to 7 or 8 Hz and rapidly fell at 8 or 9 Hz in epilepsy patients. We can speculate that the traditional theta frequency band setting at 4–8 Hz might be inappropriate to detect exact theta peak or paroxysmal activity in the theta band, especially centered around 7 or 8 Hz, and the frequency band setting at 5–9 or 5–10 Hz might be appropriate for these "high" theta activities, as already mentioned in some previous studies [26–28].

In this study, we tried to evaluate the reliability of eLORETA kurtosis analysis. For this purpose, due to the importance of theta activity in epilepsy patients as mentioned above, we set the bandpass filter at traditional frequency band settings (1–4, 4–8, 8–15, 15–30, and 30–60 Hz) and 5–10 and 20–70 Hz and performed eLORETA kurtosis to compare the source localization of paroxysmal activity with that of visual interpretation of EEG data and CSD analysis of eLORETA in focal epilepsy patients.

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Fig. 1. The results of patient 1. **a** EEG waveform in interictal recordings at the beginning of the follow-up. **b** EEG eLORETA CSD analysis. **c** EEG eLORETA kurtosis analysis.

(Figure continued on next page.)

Methods

Subjects

Three drug-naive patients with temporal lobe epilepsy (mean age 75.0 ± 3.56 years, 1 male and 2 females) were recruited at the Neuropsychiatry Department of Kansai Medical University. Their seizures were classified as a focal impaired awareness in accordance with the International League Against Epilepsy 2017 Operational Classification of Seizure Types Basic Version. They had no previous history of neurological and psychiatric disease, and no cerebral organic abnormality which causes epilepsy was recognized on magnetic resonance imaging (MRI), such as severe cerebral infarction or hemorrhage. Since all subjects included did not take any medication, EEG data analyzed by eLORETA kurtosis were measured before treatment with any drugs, after which patients were treated with antiepileptic drugs, and seizure symptoms were well controlled. The Institutional Ethical Review Board of Kansai Medical University approved the study and written informed consent as required by the Helsinki Declaration was obtained from the participants.

EEG Recording and Data Acquisition

EEG data were recorded using a digital EEG system with 19 channels (EEG-1100, Nihon Kohden, Inc., Tokyo, Japan), with the electrodes placed according to the International 10–20 System (Fp1, F3, C3, P3, O1, F7, T7, P7, Fp2, F4, C4, P4, O2, F8, T8, P8, Fz, Cz, Pz). The EEG data at resting state with eyes closed were analyzed. The EEG was digitized at sampling intervals of 500 Hz and not filtered. Each EEG session lasted about 1 h, and all 10-s artifact-free periods containing epileptic paroxysmal activity obtained during visual inspection of the data were used for eLORETA CSD analysis and kurtosis source localization analysis. Two certified electroencephalographers evaluated the patients' EEG at the different times and were blind to each other's ratings.

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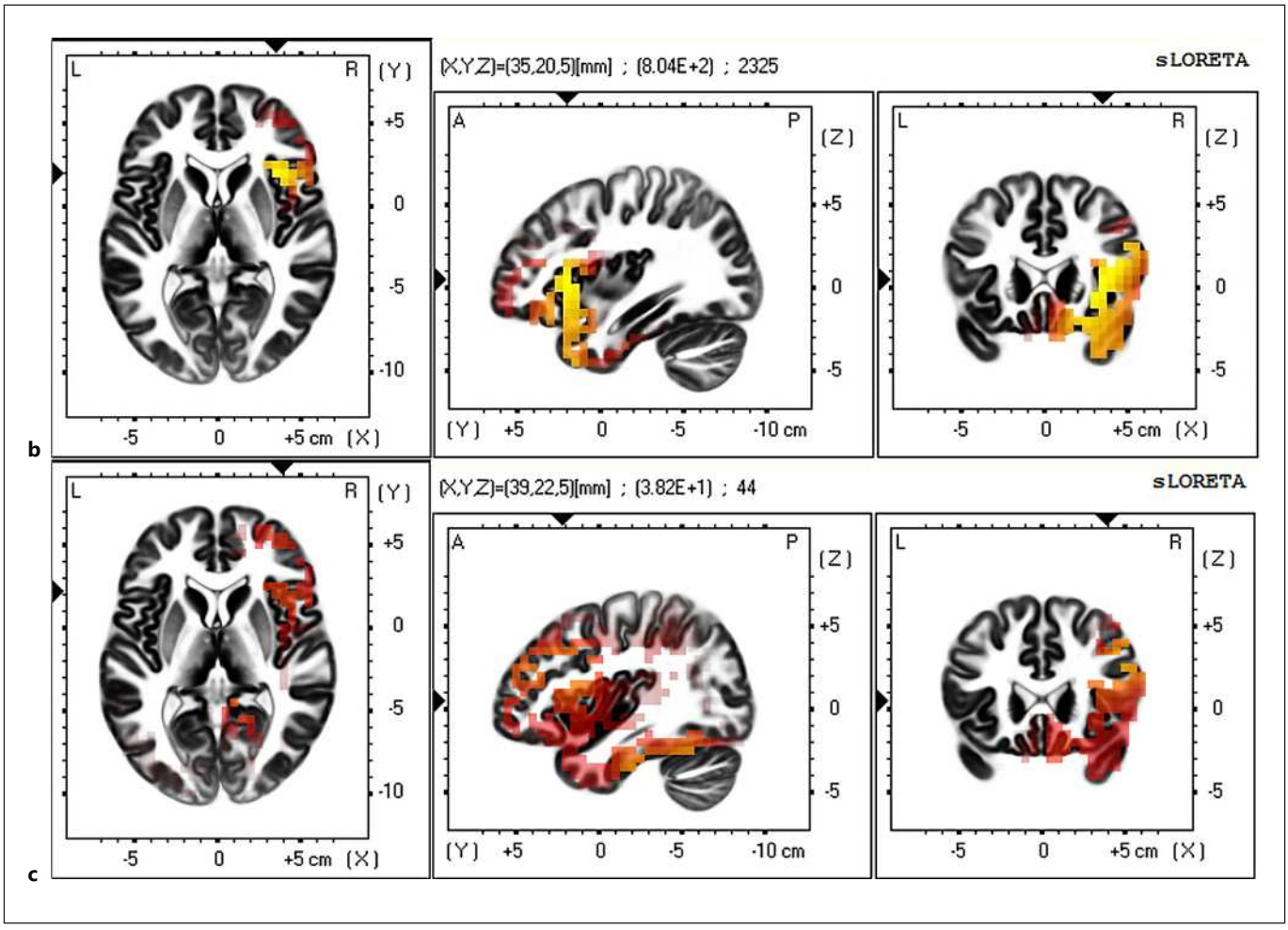

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CSD Analysis of eLORETA

eLORETA is an EEG analysis method for displaying the 3-dimensional image of the distribution of brain electrical activity sources devised by Pascual-Marqui et al. [8]. This analysis method allows the depiction of the origin of brain electrical activity obtained on the scalp as tomography. CSD analysis of eLORETA is based on a distinct, linear, weighted minimum norm inverse solution. In the eLORETA system, the analyzed space was limited to the cortical gray matter, separated by 6,239 voxels at 5 × 5 × 5 mm spatial resolution. As a head model of eLORETA, the Montreal Neurological Institute average MRI brain (MNI152) was used. For equivalent current dipole (ECD) analysis, we applied eLORETA at the exact one time point of maximum amplitude of the epileptic paroxysmal activity for each patient, which was evaluated by 2 certified electroencephalographers.

Kurtosis Analysis of eLORETA

Kurtosis is a statistical measure of representing the sharpness of the probability density function of a random variable and the frequency distribution. Compared to the normal distribution, it can be judged that if the kurtosis is larger, it has a sharper peak and a longer thick tail, and if the kurtosis is smaller, it has a more roundish peak and a shorter thin tail. Spiky paroxysmal activity in eLORETA brings large positive kurtosis values, while rhythmic cortical activity is associated with low kurtosis values. Kurtosis analysis was adapted to this program based on a program written in MATLAB (The MathWorks, Natick, MA, USA). As preprocessing of the kurtosis analysis, the EEG data were digitally filtered in traditional frequency band settings (1–4, 4–8, 8–15, 15–30, and 30–60 Hz), the frequency band from 5 to 10 Hz to see the paroxysmal activity in the theta band, and the frequency band from 20 to 70 Hz to see the same spike activity as in the MEG SAM(g2) analysis. For kurtosis analysis, the EEG data of time windows of 10 s, each including 1 paroxysmal activity which was previously evaluated by 2 certified electroencephalographers and preprocessed by the 5–10 Hz bandpass filter, were analyzed.

Results

The eLORETA kurtosis analysis of EEG data preprocessed by bandpass filtering from 20 to 70 Hz and traditional frequency band settings (1–4, 4–8, 8–15, 15–30,

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Fig. 2. The results of patient 2. **a** EEG waveform in interictal recordings at the beginning of the follow-up. **b** EEG eLORETA CSD analysis. **c** EEG eLORETA kurtosis analysis.

(Figure continued on next page.)

and 30–60 Hz) did not show any discrete paroxysmal source activity compatible with the results of the CSD analysis of eLORETA. The eLORETA kurtosis analysis filtered from 5 to 10 Hz showed the following paroxysmal activity in the theta band.

The results of the visual inspection of the EEG waveform in the first subject revealed spiky paroxysmal activity with phase reversal at electrode T4 or F8, indicating a right temporal source of epileptic activity (Fig. 1a). For the first subject, the results of CSD analysis indicated that CSD increased in the right frontotemporal lobe and right inferior frontal gyrus when the action potential was mapped firmly to the paroxysmal activity (Fig. 1b). eLORETA kurtosis analysis at 5–10 Hz showed high kurtosis values in the right frontotemporal lobe and right inferior frontal gyrus in the first subject (Fig. 1c).

For the second subject, visual analysis identified epileptic paroxysmal activity with phase reversal at electrode T5 (Fig. 2a). CSD analysis estimated the source in the left anterolateral region of the parietal cortex and the left superior temporal cortex, accurately fitting the analysis points to the paroxysmal activity (Fig. 2b). eLORETA kurtosis analysis at 5–10 Hz found sources of high kurtosis values in a portion of the parietal cortex and weakly in the superior temporal cortex (Fig. 2c).

For the third subject, visual inspection showed a spiky paroxysmal activity with phase reversal at electrode T4 as an epileptic source (Fig. 3a). The results of CSD analysis

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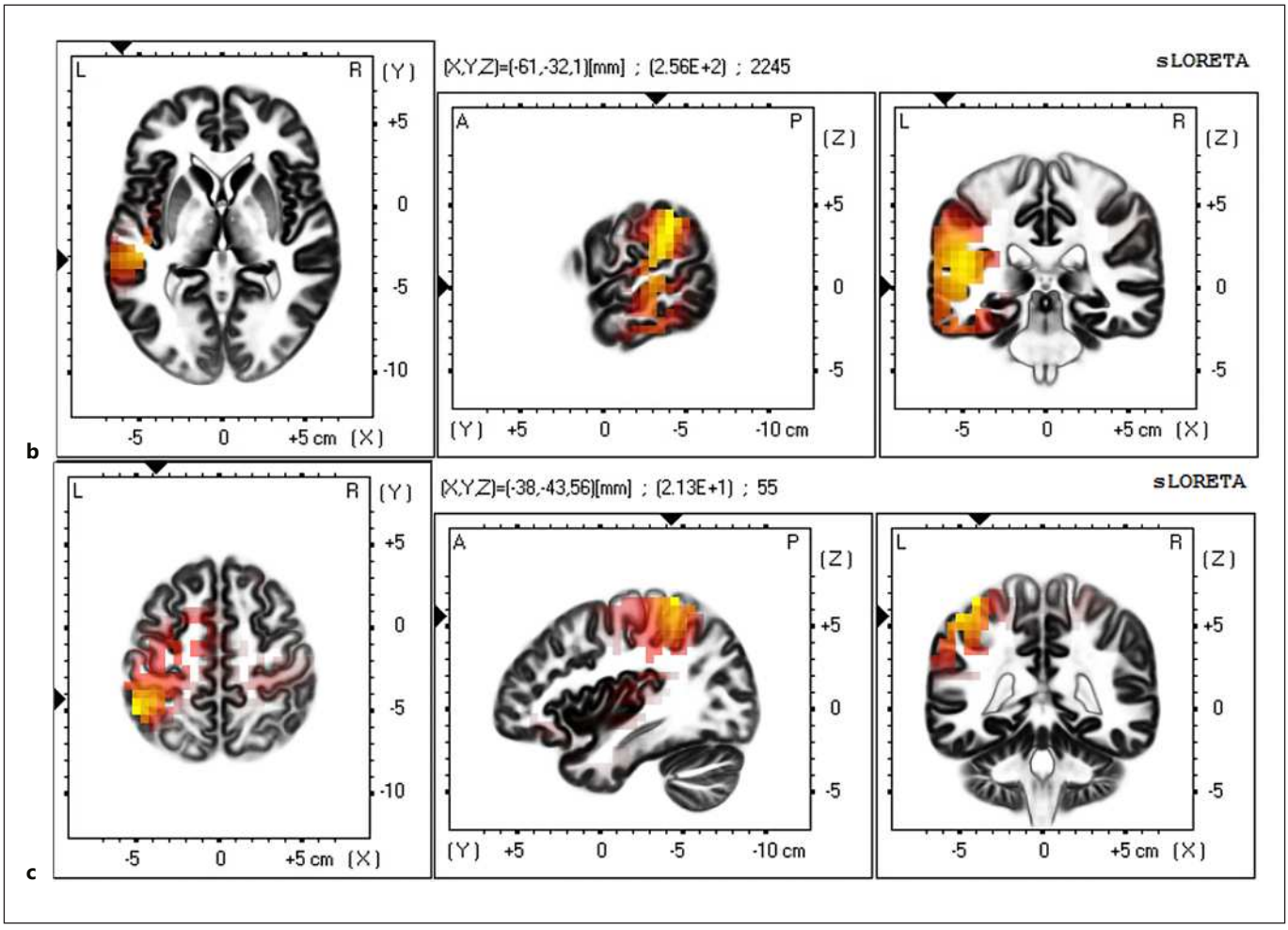

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localized the source in the right temporal lobe (Fig. 3b). eLORETA kurtosis analysis of 5–10 Hz identified high kurtosis values in the right temporal lobe (Fig. 3c).

In all 3 cases, the visual inspection results, the CSD analysis results, and the kurtosis analysis results at 5–10 Hz were all consistent with each other.

Discussion

In this study, the results of eLORETA kurtosis source localization of paroxysmal activity were compared with those of visual inspection and CSD analysis in 3 focal epilepsy patients with complex partial seizures. Although overlapping of kurtosis and CSD results was not complete, the results of eLORETA kurtosis source localization at 5–10 Hz and CSD results showed consistent results in the same area. Unlike CSD analysis at the time points of epileptic spikes which had to be detected by certified electroencephalographers, the eLORETA kurtosis analysis at 5–10 Hz can utilize the EEG data in time windows of 10 s without any evaluation of the peak of paroxysmal activity.

Kurtosis analysis has been reported in several MEG studies which applied this method to interictal MEG data in epilepsy patients and showed its capability and usefulness [15–23]. Although MEG has several advantages, such as high temporal resolution and better spatial resolution than EEG, it also has some critical disadvantages for clinical application, such as the huge device size, the expensive running costs, and the vulnerability to environmental magnetic noise. EEG has been widely used in clinical practice for more than decades to support the clinical diagnosis and management of epilepsy. This usefulness arises mainly from the fact that EEG can directly measure brain electrical activity noninvasively and inex-

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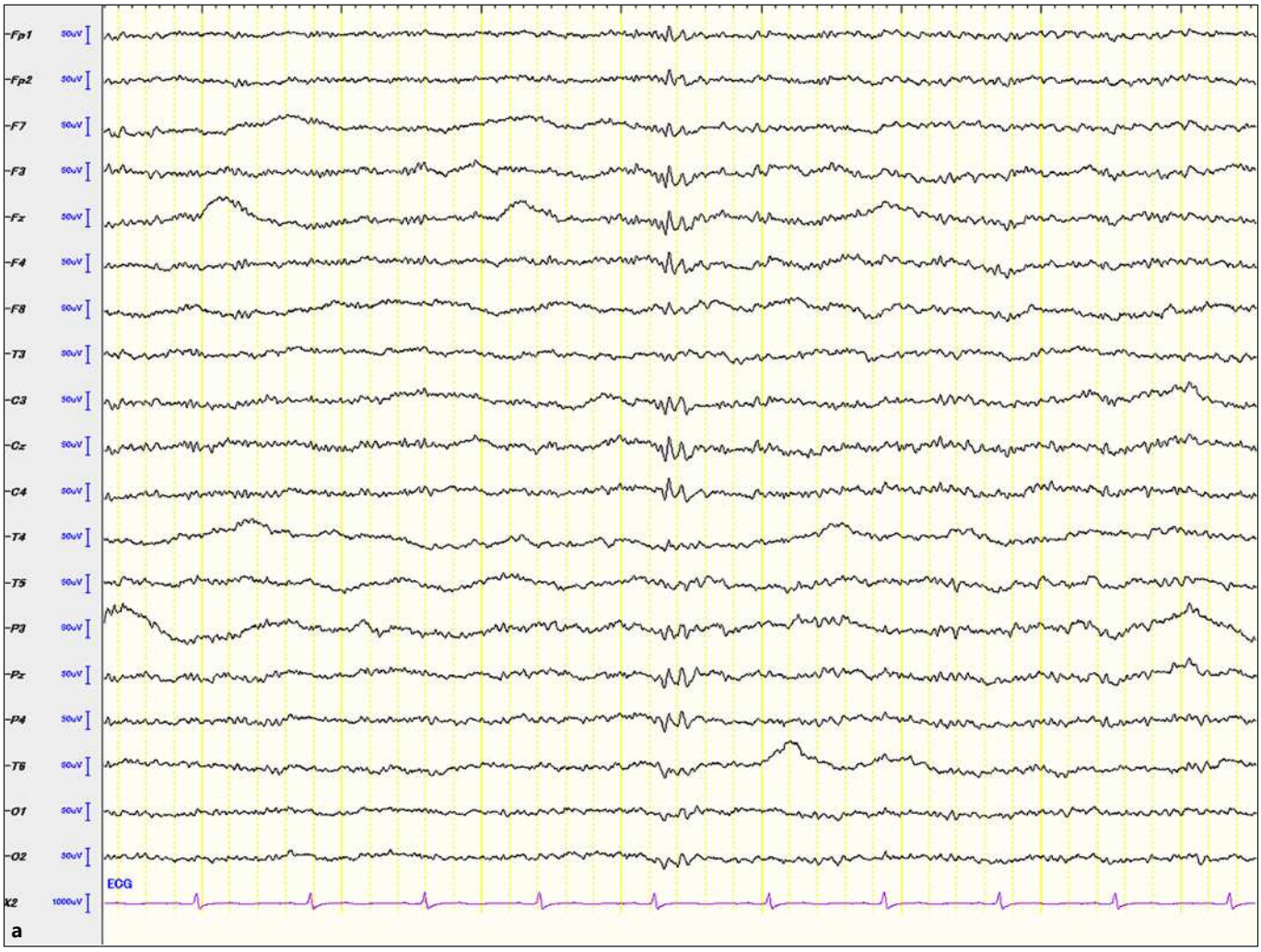

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Fig. 3. The results of patient 3. **a** EEG waveform in interictal recordings at the beginning of the follow-up. **b** EEG eLORETA CSD analysis. **c** EEG eLORETA kurtosis analysis.

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pensively. Our study suggests that kurtosis analysis applied to scalp EEG and eLORETA analysis seems to be a quite useful and promising method for the clinical application to epilepsy.

Kurtosis analysis has 2 major advantages: firstly, it does not rely on a priori knowledge about the localization of the epileptic activity, particularly when the number of spikes is unknown. Secondly, while CSD analysis requires strict matching of spike latency in the multichannel EEG data, which consumes much time and effort even when read by certified electroencephalographers, in kurtosis analysis, the source can be estimated in EEG data in the range of about 10 s or longer without identifying the spike. The source estimation of the epileptic abnormal discharge using EEG data with such a wide time range can be clinically applied to the automatic analysis function of the spike wave detection in EEG examination in the near future.

In this study, to elucidate paroxysmal activity in the theta band in epilepsy patients, as mentioned above, we set the bandpass filter at 5–10 Hz and performed eLORETA kurtosis in focal epilepsy patients. It is well known that scalp EEG suffers from anatomical brain structures which distort the current source distribution and act as a high-cut filter above beta and gamma bands. We can assume that these EEG signal characteristics might cause differences in frequency settings between MEG SAM(g2) and eLORETA kurtosis analysis.

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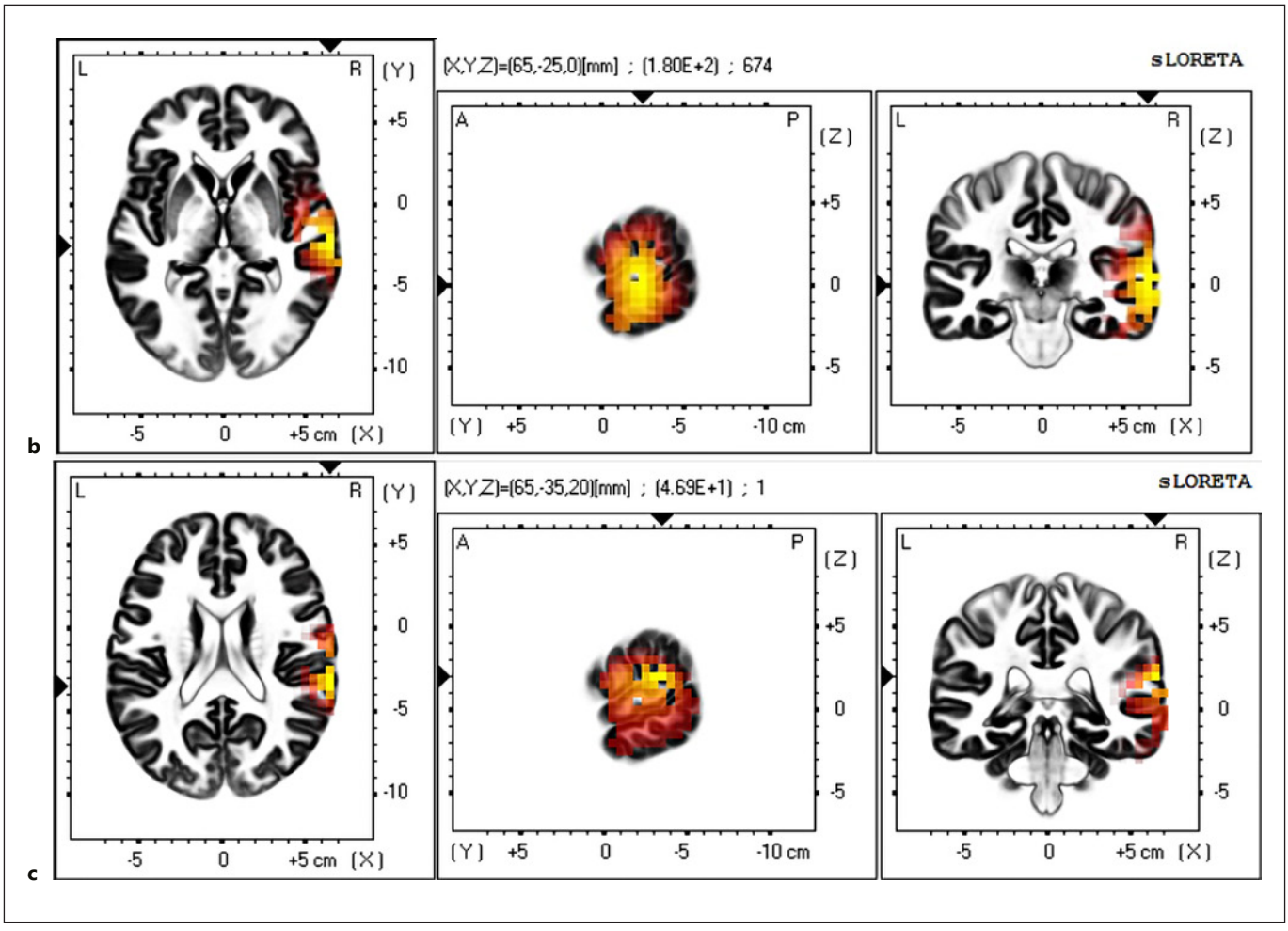

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Several limitations of this study should be acknowledged. Firstly, this was a pilot study, and the sample size of 3 subjects was too small to evaluate the new algorithm. In order to introduce this kurtosis method as a novel approach for finding spikes in epileptic EEG, which works better than traditional CSD analyses, the method should be applied to more recordings with statistical comparisons to ensure its efficacy. More important and significant results might be obtained if the number of participants increased, for example by using a database of epilepsy patients. By accumulating subjects, we would like to try to improve the accuracy of estimation, expand the range of adaptation of epilepsy cases, and extend analysis time range. Secondly, because of our search at the outpatients' clinic, all 3 subjects were accidentally rather elderly epilepsy patients who met the conditions listed in the Methods section. In the future application, we should widen the age range of subjects. Third, this analysis was analyzing EEG data including relatively few spikes. This kurtosis analysis was not suitable for EEG including too many artifacts and spikes, such as in a generalized convulsive status epilepticus.

In conclusion, our findings suggested that the eLORETA kurtosis analysis of EEG data might be useful for the identification of the sources of spiky paroxysmal activity in epilepsy patients. Since EEG is widely used in the clinical setting of epilepsy compared to MEG, it is promising that eLORETA kurtosis analysis can be applied to epileptic activity mapping. In the future, it is necessary to accumulate a higher number of subjects and to improve this analysis method.

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Statement of Ethics

The Institutional Ethical Review Board of Kansai Medical University approved the study and written informed consent as required by the Helsinki Declaration was obtained from the participants.

Disclosure Statement

The authors declare that there is no conflict of interest.

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